REMARKS/ARGUMENTS

In the December 10, 2004 Office Action, the Examiner rejected claims 31-48 pending in the application. This response amends claims 32, 36, and 45 for consideration. After entry of the foregoing amendments, claims 31-48 (2 independent claims; 18 total claims) remain pending in the application. Reconsideration is respectfully requested.

The Examiner first rejected claims 32 and 36-47 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner stated that claim 32, part (b) was vague and indefinite because the recitation "post-combination affinity reagent; and" leaves it unclear as to whether Applicant intended the claim to further include something else. In response to the Examiner's rejection, Applicant has amended claim 32 so that the claim ends after "post-combination affinity reagent." In addition, with respect to claim 36, the Examiner stated that claim 36 is vague and indefinite because it is unclear if a single type of antibody binds to different types of species or whether there are different types of antibodies specific for different types of species. In response, Applicant has amended claim 36 to address the Examiner's concern. Finally, the Examiner stated that in claim 45, the recitation "the mass spectrometric mixture" lacked sufficient antecedent basis. In response to the Examiner's rejection, Applicant has amended the claim to provide adequate antecedent basis.

Claims 31, 32, 34 and 45 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Papac et al., (Direct Analysis Of Affinity-Bound Analytes By MALDI/TOF MS, Anal. Chem. 1994, 66, 2609-2613). In particular, the Examiner states that Papac (Analytical Chemistry) discloses a method for mass spectral identification and detection of analytes separated by immunoaffinity chromatography. The Examiner further states that Papac discloses antibody immobilized to agarose beads and use of affinity columns. Moreover, the Examiner contends that Papac discloses passing a solution of horse heart cytrochrome c (a physiological specimen) through the column and that the immobilized antibody captures the cytochrome c (post-combination affinity reagent) (page 2611). The Examiner further states that Papac discloses washing to remove any unbound cytochrome c, that the sample is mixed with beads and centrifuged and that supernatant is removed, and that a matrix containing formic acid is added and a supernatant then tested by mass spectrometry (page 2611, column 1 & page 2613, column 2). The Examiner further states that Papac discloses that the captured analyte was released

(eluted). Applicants respectfully traverse this rejection.

Papac (Analytical Chemistry) discloses the direct analysis of a known affinity-bound analyte using MALDI/TOF MS. In particular, Papac discloses using horse heart cytochrome c (a sample with a known analyte). In contrast, Applicants' invention is directed to a method for determining the identity of an analyte species in a physiological specimen, not a specimen where the analyte is already known. Nowhere in Papac (Analytical Chemistry) is there the disclosure or even the suggestion of analyzing a physiological specimen to determine whether or not it contains an analyte species and then determining the identity of that analyte species. In addition, Papac fails to disclose releasing an isolated analyte species by eluting the analyte species from an antibody and then detecting a presence of the isolated and released analyte species using a mass spectrometer to determine whether the analyte species was present in the physiological specimen. Instead, aliquots of beads containing the predetermined analyte were removed from the column for performing MALDI/TOF analysis (see page 2611, column 1, first paragraph). The discussion under mass spectrometry on page 2611, first paragraph of the Papac reference merely describes how the sample aliquots of beads containing the known analytes were prepared for performing mass spectrometry. Further, this is clearly confirmed in the results and discussion section which states "purification was necessary before binding the antibody to the affinity support. To accomplish this purification, cytochrome c was first bound to the affinity support (see Experimental Section). The crude antibody solution was passed through the column, and a 1-μL aliquot of the column bed was used to acquire the MALDI/TOF spectrum shown in Figure 1A." (Papac, page 2611, bottom of column 1, top of column 2). In contrast, in Applicants' invention, the analyte species is released by eluting it from the antibody and a released analyte species is detected using a mass spectrometer to 1) determine whether the analyte species is present in the physiological specimen and 2) to determine the identity of the analyte species using molecular weight analysis.

Claims 33 and 35 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Analytical Chemistry) in view of Rampal et al., U.S. Patent No. 5,437,979, issued August 1, 1995 (hereinafter "Rampal"). Although the Examiner concedes that Papac differs from the instant invention in failing to teach combining the affinity reagent with a specimen using a micropipette tip in which there is a filter element which retains the affinity reagent, the Examiner contends that Rampal discloses a micropipette tip in which solid substrates are retained by porous frits. The Examiner further contends that Rampal discloses that these solid substrates

comprise immobilized reactants which bind to an analyte of interest and that use of the micropipette tips in this manner minimizes exposure of the solid phase to the surroundings by retaining the solid phase in an almost fully enclosed environment thereby enhancing reliability, reproducibility and safety. Therefore, the Examiner contends that it would have been obvious to one of ordinary skill in the art to incorporate the beads of Papac et al. into a micropipette such as taught by Rampal because Rampal discloses that these pipette tips can be used in reaction assays and also minimizes the exposure of the solid phase to the surroundings by retaining the solid phase in an almost fully enclosed environment thereby enhancing reliability, reproducibility and safety. Applicants respectfully traverse this rejection.

Rampal discloses performing a sequential series of reactions on an immobilized chemical species while the pipette tips are mounted on a robot. In contrast, Applicants' invention involves only one reaction, namely the antibody/antigen interaction, if the antibody/antigen interaction can even be considered a reaction. Applicants' inventive method does not involve the sequential series of reactions that are disclosed in Rampal. In Rampal, the chemical species subjected to the reactions of the biospecific binding member is still in the pipette tip. If the teachings of Rampal were to be incorporated in Applicants' claimed method, it is at this stage that the biospecific binding member would undergo mass spectrometry. Clearly, Applicants do not place a pipette tip containing a biospecific binding member into the mass spectrometer. Later Rampal discloses an additional step where reactants are separated from the pipette tip which indicates that a minimum of three reactions are needed for the process disclosed by Rampal. In contrast, Applicants' inventive method captures and elutes the analyte species in two steps. Moreover, Rampal teaches away from Applicants' inventive method by targeting the chemical species for separation rather than the interactants. This difference is of great practical importance because of interferences in the mass spectrum arising from the immobilized antibody (which would be Rampal's chemical species). In fact, the process disclosed in Rampal teaches away from MSIA in how to perform a biospecific assay and how to elute a retained protein. Accordingly, it would not have been obvious to one of ordinary skill in the art to incorporate the beads of Papac et al. into a micropipette tip such as taught by Rampal to arrive at Applicants' claimed invention.

Claims 36, 37, 39 and 46 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Analytical Chemistry) in view of Awata et al. (Immunoaffinity Extraction of 4-Hydroxy-2-(4-methylphenyl) benzothiazole and Its Metabolites for Determination by Gas chromatography-Mass Spectrometry, Biol. Pharm. Bull. 17(6) 843-845 (1994)). In particular,

although the Examiner concedes that Papac differs from the instant invention in failing to teach the affinity reagent having a specific affinity for more than one analyte, the Examiner contends that Awata discloses antibodies which have a broad spectrum of affinity, not only for an analyte of interest but also for metabolites of the analyte. The Examiner further contends that Awata discloses that this type of antibody provides for the simultaneous extraction of related substances and for their simultaneous determination. Therefore, the Examiner contends that it would have been obvious to one of ordinary skill in the art to incorporate antibodies as taught by Awata into the method of Papac because Awata shows that this type of antibody provides for the simultaneous extraction of related substances and for their simultaneous determination and further because Papac teaches that determination of analytes and that immunoaffinity separation and purification techniques based upon these methodologies are of increasing importance in biotechnology. Applicants respectfully traverse this rejection.

As previously set out above, Papac fails to disclose using mass spectrometry for identifying an unknown analyte as claimed by the instant application. The analyte which is analyzed in Papac is already known. Moreover, Papac fails to disclose a method for capturing and isolating an analyte species from a physiological specimen using an affinity reagent that includes an antibody immobilized onto a solid substrate, releasing the isolated analyte species by eluting analyte species from the antibody, and detecting the presence of the isolated and released analyte species using mass spectrometry. (See above discussion with reference to the Examiner's 35 U.S.C. §103(a) rejection based on Papac). Moreover, Awata fails to disclose these same required elements of Applicants' claims in that Awata incorporates gas chromatography-mass spectrometry and does not use mass spectrometry alone for performing separation and detection of an analyte. Accordingly, in that neither Papac nor Awata, either alone or in combination, discloses each of the elements of Applicants' claimed invention, Applicants' claims cannot be rendered obvious in light of these references.

Claims 38 and 40 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac (Analytical Chemistry) and Awata in view of Rampal. In particular, the Examiner states that it would have been obvious to one of ordinary skill in the art to incorporate the modified beads of Papac into a micropipette such as taught by Rampal because Rampal discloses that these pipette tips can be used in reaction assays and also minimizes exposure of the solid phase to the surroundings by retaining the solid phase in an almost fully enclosed environment, thereby enhancing reliability, reproducibility and safety. Applicants respectfully traverse this rejection.

In response to the Examiner's contentions, Applicants direct the Examiner to Applicants' arguments refuting the Examiner's 35 U.S.C. §103(a) rejection of claims 33 and 35 and herein incorporate those arguments by reference in their entirety.

Claims 41 and 47 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac and Awata in view of Mackert et al. (Journ. Of Chromatography, 494 (1989) 13-22) or Chiabrando et al. (Journ. Of Chromatography 495 (1989) 1-11). In particular, the Examiner states that Mackert and Chiabrando teach immobilizing a plurality of different antibodies to capture and isolate different analytes. Accordingly, the Examiner contends that it would have been obvious to one of ordinary skill in the art to incorporate a plurality of different antibodies as taught by Mackert or Chiabrando into the modified method of Papac because Awata specifically teaches that it is known in the art to co-immobilize several characteristic antibodies and Awata specifically refers to Mackert and Chiabrando. Therefore the Examiner asserts that one of ordinary skill in the art would have a reasonable expectation of success incorporating co-immobilized different antibodies for separating and detecting analytes of interest. Applicants respectfully traverse this rejection.

Neither Mackert or Chiabrando disclose using mass spectrometry for identifying an unknown analyte nor do they disclose a method for capturing and isolating an analyte species from a physiological specimen using an affinity reagent that includes an antibody immobilized onto a solid substrate, releasing the isolated analyte species by eluting the analyte species from the antibody, and detecting the presence of the isolated and released analyte species using mass spectrometry. Moreover, as previously discussed above, neither Papac or Awata discloses these required elements of Applicants' claims. Accordingly, in that neither Papac, Awata, Mackert, or Chiabrando, either alone or in combination, disclose all of the elements of Applicants' claims, Applicants' claims cannot be rendered obvious by these references.

Claims 42, 43 and 44 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Papac and Awata in view of Mackert or Chiabrando as applied to claims 36, 37, 39 and 41 above, and further in view of Rampal. In particular, the Examiner contends that it would have been obvious to one of ordinary skill in the art to incorporate the modified beads of Papac into a micropipette such as taught by Rampal because Rampal discloses that these pipette tips can be used in reaction assays and also minimizing exposure of the solid phase to the surroundings by retaining the solid phase in an almost fully enclosed environment, thereby enhancing reliability, reproducibility and safety. Applicants respectfully traverse this rejection. In response to the

Examiner's rejection, Applicants direct the Examiner to their arguments set out in response to the Examiner's rejection of claims 33 and 35 under 35 U.S.C. §103(a) and the Examiner's rejection of claims 41 and 47 under 35 U.S.C. §103(a) and herein incorporate those arguments by reference in their entirety.

Claim 48 stands rejected under 35 U.S.C. §103(a) as being unpatentable over Papac in view of Williams et al., U.S. Patent No. 5,135,870. In particular, although the Examiner concedes that Papac fails to specifically teach adding a laser desorption/ionization agent to the released and isolated analyte species to form a mass spectrometric mixture, the Examiner contends that Williams discloses that prior to analysis by mass spec a sample should be volatized in a liquid or solid matrix. The Examiner further states that Williams teaches that this provides for the mass spectrometric analysis of proteins without fragmentation or degradation, or with controlled fragmentation. Therefore, the Examiner contends that it would have been obvious to one of ordinary skill in the art to incorporate a matrix as taught by Williams with a supernatant containing the analyte of Papac because Williams shows that this provides for the mass spectrometric analysis of proteins without fragmentation or degradation, or with controlled fragmentation. Applicants respectfully traverse this rejection.

Williams fails to disclose using mass spectrometry for identifying an unknown analyte. Williams also fails to disclose a method for capturing and isolating an analyte species from a physiological specimen using an affinity reagent that includes an antibody immobilized onto a solid substrate, releasing the isolated analyte species by eluting analyte species from the antibody, and detecting the presence of the isolated and released analyte species using mass spectrometry. Moreover, as previously discussed above, Papac also fails to disclose these elements. Accordingly, in that neither Papac or Williams, either alone or in combination disclose each of the elements of Applicants' claim, Applicants' claim 48 could not be obvious in light of Papac and Williams.

In view of the foregoing, Applicants respectfully submit that all of the pending claims fully comply with 35 U.S.C. §112 and are allowable over the prior art of record. Reconsideration of this application and allowance of all pending claims is earnestly solicited. Should the Examiner wish to discuss any of the above in greater detail or deem that further amendments should be made to improve the form of the claims, then the Examiner is invited to telephone the undersigned at the Examiner's convenience.

Moreover, in that the instant application has been pending for several years with multiple

Office Actions rejecting Applicants' claims, Applicants request that the Examiner allow this application to move forward to the Board of Patent Appeals and Interferences in the event that the Examiner once again fails to find allowable subject matter. In other words, Applicants specifically request that in the event the Examiner fails to find allowable subject matter that the Examiner refrain from withdrawing the final rejection and instead allow this application to move on in the appeal process.

Respectfully submitted,

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